tumor, and wherein the vector is capable of expressing the tumor-interacting protein in a mammalian cell.

REMARKS

Amendments were made to more clearly claim the invention. No new matter is added herewith. Changes to the claims can be seen on a separate page entitled VERSION WITH MARKINGS TO SHOW CHANGES MADE following the signature page. Insertions are underlined.

Allowable Subject Matter

Applicants wish to note that Claims 1-10, 12-16, 18-21, 24, 25, 27-29, 31-34, 36-38, 47-53, and 57-74 are pending. Objections and/or rejections have been raised in regard to Claims 1-10, 12-16, 18-21, 24, 25, 27-29, 31-34, 36-38, 47-53, 57-66, 71, and 72. However, no objection or rejection has been raised in regard to Claims 67-70 and 73-74. Thus, Applicants assert that Claims 67-70 and 73-74 recite allowable subject matter. Applicants respectfully request that the Examiner confirm that these claims are allowable.

Objection to Drawings

In response to the Draftsperson's objections to the drawings, Applicants file herewith a set of formal drawings. Applicants respectfully request withdrawal of the objection on this basis.

Double Patenting

The Examiner asserts that Claims 58 and 59 are identical claims, and if Claims 58 were found to be allowable, Claim 59 would be objected to under 37 C.F.R. § 1.75. Applicants note that this matter was addressed in the amendment filed April 24, 2002, in which Applicants cancelled Claim 59, and is confirmed by Examiner's comments on page 3, paragraph 3 of the present Office Action. Therefore, Applicants respectfully assert that any objection to Claim 59 is moot in light of the amendment.

Claim Rejection Under 35 U.S.C. § 112, first paragraph

Claims 20, 21, 24, 25, 27, 28, 29, 33, 34, 38, 49, 50, 51, 52, 53, 58, and 59 were rejected under 35 U.S.C. § 102, first paragraph, as containing subject matter which was not described in

such a way as to enable one skilled in the art. The Examiner maintains that the claims are not enabled because the "specification merely discloses instructions of how to construct vectors, and prophetic examples of how the vectors may be delivered to tumors and possible animal models." The Examiner asserts that the specification does not disclose any evidence that the vectors actually deliver the polynucleotide(s) to the tumor or that the methods are effective at treating or ameliorating cancer.

The Examiner acknowledges that the specification shows that a vector can be delivered to a tumor by intra-tumoral delivery and that a vector can have a cytotoxic effect on cells in vitro. Applicants have provided a Declaration by Dr. Miles Carroll which demonstrates intratumoral delivery of adenoviral vectors encoding scFv proteins specific to 5T4 and expression of the vectors in mice. The Declaration further demonstrates specific expression of B7-scFv in the sera of Balb/c mice and expression of B7-scFv in a tumor following intratumoral delivery using the AdB7-scFV vector in mice. The Declaration showed that the scFV-Hγ1 fusion protein is able to direct cytotoxicity against cells expressing the 5T4 antigen at the cell surface, wherein the targeted cells are in vitro. The Declaration also showed that the genetic delivery of a construct encoding the scFv-Hγ1 fusion protein using the MLV-LscFV Hγ1 to cancer cells leads to secretion of the protein from the cells and their binding to the cell surface, wherein the cells are in vitro. The Applicants have shown successful delivery of polynucleotides *in vitro* and *in vivo*. Thus, Applicants assert that the presently claimed invention is enabled, and Applicants respectfully request withdrawal of the rejection on this basis.

Claim Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1-10, 12-16, 18-21, 24, 25, 36-38, 47-50, and 60 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner notes that Claim 1 lacks antecedent basis for the term "the tumor". Applicants have amended Claim 1 to provide antecedent basis and respectfully request withdrawal of the rejection on this basis.

Claim Rejection Under 35 U.S.C. § 103(a)

Claims 1-10, 12-16, 18, 20, 27, 34, 36, 37, 47-49, 51, 57, 60-65, 71, and 72 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Anderson et al. in view of Myers et al. The Examiner states that Anderson does not teach a vector that binds to a trophoblast cell surface

antigen or that the trophoblast cell surface antigen to which the vector binds is 5T4. The Examiner asserts that Myers teaching of the isolation of a cDNA encoding 5T4 Oncofetal Trophoblast Glycoprotein and the indication that 5T4 is expressed on fetal trophoblast membranes and carcinomas is sufficient to provide one of ordinary skill in the art the ability to combine these references to make and use the presently claimed invention. The Examiner alleges that Forsberg teaches that 5T4 can be used to target therapeutic molecules to several types of solid tumors and thus it would be obvious to substitute the vector of Anderson with an antibody that reacts with 5T4 as taught by Myers.

Applicants respectfully submit that a *prima facie* case of obviousness has not been established. To establish a *prima facie* case of obviousness, M.P.E.P. §§ 2142 and 2143 require three basic criteria to be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure.

Applicants assert that the combination of Anderson and Myers is not sufficient to provide one of ordinary skill in the art with the teaching and motivation to make and use the presently claimed invention. Applicants note that Anderson teaches targeting antibodies, but does not include 5T4 in that list. By excluding 5T4 from the list, Applicants assert that Anderson did not envision use of 5T4 and does not provide motivation to use 5T4 or any tumor-interacting protein which binds to a trophoblast cell surface antigen. Applicants assert that one of skill in the art would not be motivated by the teaching of Anderson to use 5T4 or any tumor-interacting protein which binds to a trophoblast cell surface antigen.

Furthermore, Applicants assert that Forsberg does not provide evidence that 5T4 can be used to target therapeutic molecules to several types of solid tumors. Fosberg et al. relates to expression of a 5T4Fab-SEch fusion protein in a prokaryotic cell (i.e. *E. coli*). The vector to which Forsberg refers (page 12431, column 2, Results section) is the vector of Dohlsten et al. (1994). This vector is a pkp865 vector which has no mammalian promoter and thus is incapable of expression in a mammalian cell. Therefore, Forsberg et al. do not teach a 5T4-Fab-SEch

fusion protein which is capable of expression in a mammalian cell. Thus, the vector taught by Forsberg is not suitable for delivery of therapeutic genes to a tumor. Applicants note that claim 1 has been amended to recite, *inter alia*, a vector wherein the vector is capable of expressing the tumor-interacting protein in a mammalian cell.

Contrary to the Examiner's assertion, Forsberg provides no evidence the 5T4 can be used to target molecules to tumors. Applicants assert that one of skill in the art attempting to make or use the presently claimed invention would not be able to combine the teachings of Anderson and Myers with a reasonable expectation of success. In addition, Forsberg does not provide evidence a reasonable expectation of success for making and using a vector comprising a polynucleotide encoding a tumor-interacting protein wherein the tumor-interacting protein binds to a trophoblast cell surface antigen on a tumor and wherein the vector delivers a second polynucleotide of interest to the tumor, and wherein the vector is capable of expressing the tumor-interacting protein in a mammalian cell. Applicants respectfully request withdrawal of the rejection on this basis.

Claims 19 and 66 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Anderson et al. in view of Myers et al. and further in view of Barber. Applicants note that the Examiner has combined three references, in addition to a fourth reference for supposed evidence, to provide a *prima facie* case for obviousness. Thus, technically, the Examiner is depending on four references to create a *prima facie* case for obviousness. Applicants assert that it would not be reasonable for one of skill in the art to combine these four references in order to provide the teaching, motivation to combine, and expectation of success of making or using the presently claimed invention. Applicants assert that the Examiner has failed to provide a *prima facie* case for obviousness.

In addition, Applicants again note that the Examiner depends on Forsberg to provide evidence of 5T4 being used to target therapeutic molecules to several types of solid tumors. However, Applicants assert that the vector taught by Forsberg is not suitable for delivery of therapeutic genes to a tumor. Fosberg et al. relates to expression of a 5T4Fab-SEch fusion protein in a prokaryotic cell (i.e. *E. coli*). The vector to which Forsberg refers (page 12431, column 2, Results section) is a pkp865 vector which has no mammalian promoter and thus is

incapable of expression in a mammalian cell. Thus Applicants assert that Fosberg can provide no evidence of a reasonable expectation of success.

Claims 31 and 32 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Anderson et al. in view of Myers et al. and Barber et al. and further in view of Willis. Applicants note that the Examiner has combined four references, in addition to a fifth reference for supposed evidence, to provide a *prima facie* case for obviousness. Thus, technically, the Examiner is depending on five references to create a *prima facie* case for obviousness. Applicants assert that it would not be reasonable for one of skill in the art to combine these five references in order to provide the teaching, motivation to combine, and expectation of success of making or using the presently claimed invention.

In addition, the Examiner is depending on Willis to provide teaching that a tumor-interacting protein is operably linked to a tumor-specific expression regulatory element, or that said tumor interacting protein further comprises an effector domain such as all or part of a cytokine, a toxin, pro-drug activating enzyme, or enzyme. Willis describes vectors which express fusion proteins encoded by a gag gene fused to a heterologous gene encoding, for example, a cytokine. However, Willis makes no suggestion that the vector encodes a tumor interacting protein operably linked to an expression regulatory element selectively functional in a cell type present within a tumor mass.

Column 7, lines 53-56, of Willis (as cited by the Examiner) gives no suggestion of the use of such expression regulatory elements, let alone how they can be used. This portion of Willis merely states that the proteins which need to be targeted can be expressed in this system. There is no teaching as to how such proteins could be targeted. Moreover, in column 8, Willis describes promoters, but there is no suggestion that tumor specific expression regulatory elements should be used. Applicants respectfully assert that the presently claimed invention is patentable over the cited art, thus Applicants respectfully request withdrawal of the rejection on this basis.

Conclusion

In view of the foregoing amendments and remarks Applicants assert that the present application is in condition for allowance. Should any issues arise which may delay prosecution

of the present application the Examiner is respectfully invited to contact the under-signed at the telephone number below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: _____ By: _____

Catherine M. Sanders
Registration No. 50,660
Agent of Record
Customer No. 20,995
(949) 760-0404

H:\DOCS\CMS\CMS-3292.DOC
111302

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Insertions are underlined.

IN THE CLAIMS:

Please amend the following claim:

1. (THREE TIMES AMENDED) A vector comprising a polynucleotide encoding a tumor-interacting protein wherein the tumor-interacting protein binds to a trophoblast cell surface antigen on a tumor and wherein the vector delivers a second polynucleotide of interest to the tumor, and wherein the vector is capable of expressing the tumor-interacting protein in a mammalian cell.